CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Dimethenamid-P

Chemical Code # 5919, **Tolerance** # 52984
SB 950 # NA

December 1, 2005

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap; no adverse effect indicated
Chronic toxicity, dog:	No data gap; no adverse effect indicated
Oncogenicity, rat:	No data gap; possible adverse effect indicated
Oncogenicity, mouse:	No data gap; no adverse effect indicated
Reproduction, rat:	No data gap; no adverse effect indicated
Teratology, rat:	No data gap; no adverse effect indicated
Teratology, rabbit:	No data gap; no adverse effect indicated
Gene mutation:	No data gap; no adverse effect indicated
Chromosome effects:	No data gap; no adverse effect indicated
DNA damage:	No data gap; no adverse effect indicated
Neurotoxicity:	No study submitted nor required at this time

Toxicology one-liners are attached.

All record numbers through 220747 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T120105
Revised by T. Moore, 12/1/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 0036; 215822**; "SAN 582H: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats"; (S.A. Ruckman, *et.al.*; Huntingdon Research Centre, Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. SDZ 335/891445; 3/1/90); Fifty Crl:CD (SD) BR rats/sex/group received 0, 100, 700 or 1500 ppm of SAN 582 H technical (lot no. 8605; purity: 91.3%) in the diet for up to two years ((M) 0, 5.1, 36, 80 mg/kg/day, (F) 0, 6.8, 49, 109 mg/kg/day). Satellite groups of 20 animals/sex were treated in the same manner for 12 months. Treatment did not adversely affect the survival of the study animals. The mean body weight gain was lower for both sexes in the 700 and 1500 ppm treatment groups betweens weeks 0 and 10 and between weeks 10 and 80 (NS, $p<0.05$ or 0.01). Mean food consumption of both sexes in the 700 and 1500 ppm groups was less than that of the controls between 0 and 10 weeks ($p<0.05$ or 0.01). The hematology and urinalysis evaluations did not reveal an apparent treatment-related effect. In the clinical chemistry examinations, the serum gamma glutamyl transpeptidase activity level was elevated for the males in the 1500 ppm group throughout the study ($p<0.05$ or 0.01). Although the mean serum cholesterol levels for the females in the 1500 ppm group were elevated above those of the controls after 13 and 104 weeks of treatment ($p<0.05$ or 0.01), there was no consistent pattern of effect. In the ophthalmology examination, there was an increased incidence of posterior capsular opacity for both sexes in the 1500 ppm group after 103 weeks of treatment ((M) 0: 4/20 vs. 1500: 13/32, (F) 0: 4/26 vs. 1500: 11/34). The body weight-adjusted means for the liver of the females in the 700 and 1500 ppm after 52 weeks and for the females in the 1500 ppm group after 104 weeks were greater than those values for the controls ($p<0.05$ or 0.01). In the histopathological examination, there was an increased incidence of benign and malignant tumors in the liver of the 1500 ppm males (0: 0/50 vs. 1500: 4/50). There was an increased incidence of tubular adenomas in the ovaries of the 1500 ppm females (0: 2/50 vs. 1500: 6/50). For non-neoplastic effects, a dose-response in the incidence of bile duct hyperplasia was noted for the females (0: 3/50 vs. 100 9/50, 700: 11/50, 1500: 20/50). In the liver of the 700 and 1500 ppm males, there was a greater incidence of circumscribed areas of altered eosinophilic hepatocytes (0: 2/50 vs. 700: 6/50, 1500: 10/50). A greater incidence of hyperplasia of the limiting ridge in the stomach was noted in both sexes of the 1500 ppm group ((M) 0: 6/50 vs. 1500: 20/50, (F) 0: 1/50 vs. 1500: 6/50). The 1500 ppm females demonstrated a higher incidence of ovarian tubular hyperplasia than did the controls (0: 12/50 vs. 1500: 22/50). An increased incidence of parathyroid hyperplasia was noted for the 700 and 1500 ppm males (0: 5/48 vs. 700: 13/42, 1500: 18/44). **Chronic Non-Neoplastic NOEL:** (M/F) <100 ppm ((M) <5.1 mg/kg/day, (F) <6.8 mg/kg/day) (based upon the increased incidence of lesions in the parathyroid of the 100 ppm males and in the liver of the 100 ppm females); **Possible adverse effect:** oncogenic response in the liver and ovaries. **Study acceptable.** (Moore, 9/30/05)

CHRONIC TOXICITY, RAT

See Rat, Combined above.

CHRONIC TOXICITY, DOG

** 52984-0176, -0035; 220747, 215821; "SAN 582H: 52-Week Oral Toxicity Study in Dogs"; (R.J. Greenough, R. Goburdhun, F. Macnaughtan; Inveresk Research International, Musselburgh EH21 7UB, Scotland; Project No. IRI-635579; 2/27/89); Four beagle dogs/sex/group received 0, 50, 250 or 1250 ppm of SAN 582H Technical (racemic mixture) (batch no. 8605; purity: 91.3%) in the diet for 52 weeks ((M): 0, 1.95, 10.1, 48.7 mg/kg/day, (F) 0, 2.10, 9.1, 49.3 mg/kg/day). The mean body weight gain of the 250 ppm males and of both sexes in the 1250 ppm group over the course of the study were less than the control values (NS). The mean food consumption of the 250 ppm females and of both sexes in the 1250 ppm group over the course of the study was less than the control values. No treatment-related effects were noted in the ophthalmology, the

hematology or the urinalysis data. The serum alkaline phosphatase activity levels were greater for the 1250 ppm males at 26 weeks of treatment ($p<0.01$) and for the 1250 ppm females at 13, 26 and 51 weeks ($p<0.01$ or 0.001). The mean liver weights (covariant with body weight) of the 1250 ppm males and the 50, 250 and 1250 ppm females were greater than the control values ($p<0.05$ or 0.01). In the histopathological analysis, periportal hepatocellular vacuolation was noted in the liver of both sexes of the 1250 ppm group ((M) 0: 0/4 vs. 1250: 2/4, (F) 0: 0/4 vs. 1250: 4/4 ($p<0.05$)). Midzonal hepatocyte hypertrophy was noted in the liver of the 1250 ppm males (0: 0/4 vs. 1250: 2/4). **No adverse effect indicated. Chronic Dietary NOEL:** (M/F) 50 ppm ((M): 1.95 mg/kg/day, (F): 2.10 mg/kg/day) (based upon the reduced body weight gain and/or food consumption of the animals in the 250 ppm group); **Study acceptable**. (Moore, 12/1/05)

ONCOGENICITY, RAT

See Rat, Combined above.

ONCOGENICITY, MOUSE

** 0038; 215834; "SAN 582H: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice"; (W.N. Hooks *et. al.;* Huntingdon Reseach Centre, Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. SDZ 346/90189; 8/24/90); Fifty two Crl: CD-1 (ICR) mice/sex/group received 0, 30, 300, 1500 or 3000 ppm of SAN 582 H technical (lot no. 8605, purity: 91.4%) in the diet for at least 94 weeks ((M) 0, 3.8, 40.8, 205, 431 mg/kg/day, (F) 0, 4.1, 40.1, 200, 411 mg/kg/day). An additional 16 animals/sex/group were included in the 0 and 3000 ppm treatment groups as satellite animals and were euthanized after 65 weeks of treatment. The mean body weight gain for both sexes in the 1500 and 3000 ppm groups was less than that of the control group during the first 52 weeks ($p<0.05$ or 0.01). The mean food consumption was not apparently affected by the treatment. The differential white blood cell count and morphology assessments did not reveal any treatment-related effects. The mean absolute liver and kidney weights of both sexes in the 1500 and 3000 ppm groups were greater than those of the control after 65 and 94 weeks of treatment (NS, $p<0.05$ or 0.01). In the histopathological evaluation, there was an increased incidence of centrilobular hepatocyte enlargement in the liver of both sexes in the 3000 ppm group after 65 weeks of treatment ((M) 0: 0/12 vs. 3000: 3/13, (F) 0: 0/16 vs. 3000: 8/15). This effect was not noted in the animals treated for 94 weeks. An increased incidence of generalized hepatocytes enlargement was evident for both sexes in the 300, 1500 and 3000 ppm groups after 94 weeks of treatment (M) 0: 3/52 vs. 300: 8/52, 1500: 9/52, 3000: 27/51, (F) 0: 0/52 vs. 300: 6/52, 1500: 15/52, 3000: 31/52). The males in the 3000 ppm treatment group also demonstrated an increased incidence of cortical mineralization in the kidney after both 65 and 94 weeks of treatment ((M) 65 weeks, 0: 0/12 vs. 3000: 3/13, 94 weeks, 0: 1/52 vs. 3000: 8/51). There was no treatment-related incidence of neoplastic lesions. **No adverse effect indicated. Chronic Dietary NOEL:** (M/F) 30 ppm ((M) 3.8 mg/kg/day, (F) 4.1 mg/kg/day) (based upon the increased incidence of hepatocyte enlargement in the livers of the 300 ppm treatment group); **no evidence of carcinogeneity was noted**; **Study acceptable.** (Moore, 7/6/05)

REPRODUCTION, RAT

** 0041; 215839; "SAN 582 H: Two-Generation Reproduction Study in the Rat"; (P. Suter, K. Biedermann, J. Th. Wilson; RCC, Research and Consulting Company AG and RCC Umweltchemie, CH 4452, Itingen, Switzerland; Project No. 201205; 5/17/90); Twenty five Wistar/HAN rats/sex/group received 0, 100, 500, or 2000 ppm of SAN 582 H technical (lot no. 8710, purity: 92.6%) in the diet for two generations. The treatment included 70 days prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation of the P generation. At that time, 25 F1 animals/sex/group were selected as parents and treated for 101 days prior to mating, followed by mating and 3 weeks each of gestation and lactation of the F2 generation. No deaths occurred during the study. The mean body weights and food consumption of the P and F1 males in the 2000 ppm group were less than the control values ($p<0.05$). The mean absolute and relative liver weights for both sexes and both generations of the 2000 ppm group were greater than the control values ($p<0.01$). There was no treatment-related effect upon the reproductive

parameters. The mean body weights of the pups in the 2000 ppm group were less than those of the control for both generations ($p<0.05$). **No adverse effect indicated. Parental NOEL:** (M/F) 500 ppm (M: 24 to 63 mg/kg/day, F: 32 to 92 mg/kg/day) (based upon reduced mean body weight and food consumption of the males in the 2000 ppm treatment group), **Reproduction NOEL:** 2000 ppm (M: 130 to 263 mg/kg/day, F: 229 to 359 mg/kg/day) (based upon the lack of a treatment-related effect at the highest dose tested), **Developmental NOEL:** 500 ppm (M: 24 to 63 mg/kg/day, F: 32 to 92 mg/kg/day) (based upon lower mean pup weights in the 2000 ppm group of both generations); **Study acceptable.** (Moore, 7/13/05)

0040; 215837; "One-Generation Reproduction Pilot Study in the Rat"; (P. Suter, P. Mladenovic, Ch. Terrier; RCC, Research and Consulting Company AG and RCC Umweltchemie, CH 4452, Itingen, Switzerland; Project No. 201194; 8/20/90); In the P generation, eight Wistar/HAN rats/sex/group received 0, 100, 300, 900 or 3000 ppm of SAN 582H Technical (batch no. 8605, purity: 91.5%) in the diet for a 4-week premating, mating (up to 20 days), and the 3-week gestation and lactation periods ((M) 0, 9.3, 27.8, 81.8, 286.5 mg/kg/day, (F) prepairing, 0, 9.5, 28.0, 89.3, 307.5 mg/kg/day; gestation, 0, 8.7, 26.3, 76.3, 270.3 mg/kg/day; lactation, 0, 16.0, 48.3, 144.0, 475.3 mg/kg/day). The F1 offspring received the dietary preparations for 1 week after weaning. The mean body weights for both sexes in the 3000 ppm group were slightly lower than those of the controls (NS). There was no treatment-related effect on food consumption. The reproduction parameters were not affected by the treatment. The viability and weaning indices for the 3000 ppm offspring were slightly less the control values, but within the historical control range. The mean body weights of the 900 and 3000 ppm offspring were less than that of the controls on days 7, 14 and 21 post-natal ($p<0.05$). **No adverse effect was indicated.** No **NOEL values were selected**, as this was not a guideline study. **Study supplemental.** (Moore, 7/11/05)

TERATOLOGY, RAT

** 0032; 215809; "Oral (Gavage) Developmental Toxicity Study of SAN 1289 H in Rats"; (R.G. York; Argus Research Laboratories, Inc., Horsham, PA; Project ID. 1819-010; 10/23/96); Twenty five mated Sprague-Dawley female rats/group were dosed orally by gavage with 0 (aqueous 0.5% carboxymethyl cellulose), 25, 150 or 300 mg/kg/day from day 6 through day 15 of gestation. No deaths resulted from the treatment. The dams in the 25 mg/kg group and above demonstrated a reduced body weight gain and lower mean food consumption over the course of the treatment period than did the control group ($p<0.01$). The fetuses in the 150 and 300 mg/kg groups exhibited delayed ossification of the skeleton which was quite likely related to maternal toxicity. Otherwise, no other developmental effects were evident. **No adverse effect indicated. Maternal NOEL:** < 25 mg/kg/day (based upon the lower body weight gain and mean food consumption by the 25 mg/kg dams); **Developmental NOEL:** 25 mg/kg/day (based upon the delayed ossification of the fetuses in the 150 mg/kg group). **Study acceptable.** (Moore, 6/10/05)

TERATOLOGY, RABBIT

** 0039; 215835; "Developmental Toxicity (Embryo/Fetal Toxicity and Teratogenic Potential) Study of SAN 582 H Administered Orally (Stomach Tube) to New Zealand Rabbits"; (A.M. Hoberman; Project ID. Argus 1319-003; 5/10/88); Twenty artificially inseminated female New Zealand White rabbits/group were dosed orally by gavage with 0 (aqueous 0.5% (w/v) carboxymethyl cellulose/HiSil), 37.5, 75, or 150 mg/kg/day of SAN 582 H technical (batch no. 8605; purity: 92.0%) from day 6 through day 18 of gestation. No deaths resulted from the treatment. The does in the 150 mg/kg group demonstrated reduced body weight gain and food consumption over the dosing period. There was an increased incidence of late resorptions/litter in the 150 mg/kg group (0: 0 vs. 150: 0.7). **No adverse effect indicated. Maternal NOEL:** 75 mg/kg/day (based upon the lower body weight gain and food consumption of the 150 mg/kg treatment group); **Developmental NOEL:** 75 mg/kg/day (based upon the increased incidence of late resorptions in the 150 mg/kg group); **Study acceptable.** (Moore, 7/8/05)

GENE MUTATION

**** 033; 215810**; "*Salmonella/Escherichia Coli* Plate Incorporation Mutagenicity Assay"; (V.O. Wagner and N. Coffman; Microbiological Associates, Inc., Rockville, MD; Study No. G95CB09.502; 3/14/96); *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2 *uvr*A were treated with SAN 1289 H Technical (lot no. 6663-50-1; purity: 96.3% (S-dimethenamid: 91.1%)) at concentrations ranging from 100 to 5000 ug/plate under conditions of +/- activation, using the plate incorporation method, for 48 to 72 hours at 37^{o} C. In a second trial, strain TA100 was treated with the test material at concentrations ranging from 100 to 5000 ug/plate under conditions of non-activation in the same manner as the first trial. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. A slight precipitation of the test material was noted at 3333 ug/plate and above. There was a treatment-related increase in the incidence of reverse mutations in the TA100 strain under conditions of non-activation. **Possible adverse effect.** The positive controls were functional. **Study acceptable**. (Moore, 6/10/05)

0033; 215811; "Bacterial Reverse Mutation Assay"; (V.O. Wagner, M.L. Klug; MA Bioservices, Inc., Rockville, MD; Study No. G97BB92.502099; 6/24/97); *S. typhimurium* strain TA100 was treated with SAN 1289 H Technical; lot no. 6663-50-1; purity: 91.1%) at concentrations ranging from 100 to 5000 ug/plate under conditions of nonactivation, using the plate incorporation method for 48 to 72 hours at 37^{o} C. Each treatment level was plated in triplicate. A slight precipitation of the test material was evident at 2000 ug/plate and above. There was no treatment-related increase in the incidence of reverse mutations in the TA100 strain under conditions of non-activation. **No adverse effect indicated.** The positive control was functional. **Study supplemental**. (Moore, 6/10/05)

** 0033; 215812; "*Salmonella Typhimurium/Escherichia Coli* Reverse Mutation Assay (Standard Plate Test and Preincorporation Test) with S-Dimethenamid Technical" (G. Engelhardt; H.D. Hoffmann; BASF, Department of Toxicology, D-67056 Ludwigshafen/Rhein, FRG; Project No. 40M0071/974027; 6/5/97); *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA were tested with S-Dimethenamid Technical (lot no. 6663-50-1; purity: 91.1%) for induction of mutations in 4 trials with and without rat liver activation. Trial 1 used plate incorporation with concentrations ranging from 20 to 5000 µg/plate. Trial 2 was limited to testing strain TA1535 under the same conditions as Trial 1 except that the treatment levels ranged from 500 to 4000 ug/plate. Trial 3 used preincubation for 20 minutes with shaking before plating at concentrations ranging from 20 to 5000 µg/plate. Trial 4 used plate incorporation in which strain TA100 was treated with the test material at concentrations ranging from 500 to 4000 ug/plate. There were triplicate plates per treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. **No adverse effect indicated.** There was no increase in the incidence of revertant colonies under conditions of either activation or non-activation. Positive controls were functional. **Study acceptable.** (Moore, 6/13/05)

** 0033; 215813; "*Salmonella Typhimurium/Escherichia Coli* Reverse Mutation Assay (Standard Plate Test and Preincorporation Test) with S-Dimethenamid"; (G. Engelhardt; H.D. Hoffmann; BASF, Department of Toxicology, D-67056 Ludwigshafen/Rhein, FRG; Project No. 40M0071/974028; 6/5/97); *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA were tested with S-Dimethenamid (Ref. Std.: RS-1289-111596; purity: 99.4%) for induction of mutations in 3 trials with and without rat liver activation. Trial 1 used plate incorporation with concentrations ranging from 20 to 5000 µg/plate. Trial 2 was limited to testing strain TA1535 under the same conditions as Trial 1 except that the treatment levels ranged from 500 to 4000 ug/plate. Trial 3 used preincubation for 20 minutes with shaking before plating at concentrations ranging from 4 to 2500 µg/plate. There were triplicate plates per

treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. **No adverse effect indicated.** There was no increase in the incidence of revertant colonies under conditions of either activation or non-activation. Positive controls were functional. **Study acceptable.** (Moore, 6/13/05)

** 0033; 215814; "CHO/HGPRT Mutation Assay"; (R.H.C. San, J.J. Clarke; Microbiological Associates, Inc., Rockville, MD; Study No. G95CB09.782; 4/5/96); Chinese Hamster Ovary (CHO-K_1-BH_4) cells were treated with SAN 1289 H Technical (lot no. 6663-50-1, purity: 96.3% (S-dimethenamid: 91.1%) for 5 hours at 37° C with and w/o activation. One trial was performed under non-activated and activated conditions, respectively with duplicate samples for each treatment level. In the non-activated trials, treatment levels ranged between 100 and 400 μg/ml. In the activated trials, treatment levels ranged from 100 to 450 μg/ml. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the forward mutation rate. **No adverse effect indicated**. The positive controls were functional. **Study acceptable**. (Moore, 6/16/05)

CHROMOSOME EFFECTS

** 0033; 215815; "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells"; (P.T. Curry, E. Schadly; Microbiological Associates, Inc., Rockville, MD; Study No. G95CB09.330; 2/23/96); Chinese Hamster Ovary cells (CHO-K_1) (CCL 61) were incubated with SAN 1289 H Technical (lot no. 6663-50-1; purity: 96.3% (S-dimethenamid: 91.1%)) at concentrations ranging from 2 to 120 μg/ml (nonactivated) or 8 to 500 μg/ml (activated) at 37° C. The non-activated samples were treated for 20 hours. The activated samples received 4 hours of treatment and an additional 16 hours of incubation. In both assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. All of the incubations were performed with duplicate cultures. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the percentage of cells with chromosomal aberrations under either assay conditions. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 6/16/05)

** 0033; 215816; "Micronucleus Cytogenetic Assay in Mice"; (D.L. Puman, R. Gudi, S.K. Poris; Microbiological Associates, Inc., Rockville, MD; Study No. G95CB09.122; 2/28/96); Five ICR mice/sex/group/time point were dosed intraperitoneally (ip) with 0, 103, 205, or 410 mg/kg of SAN 1289 H Technical (lot no. 6663-50-1; purity: 96.3% (S-dimethenamid: 91.1%)). An additional five animals were dosed at 410 mg/kg. For the positive control, five mice/sex were dosed with 60 mg/kg of cyclophosphamide. Treated animals were euthanized at 24, 48 and 72 hours after dosing. The animals which were treated with the positive control were euthanized 24 hours after dosing. Femoral bone marrow was harvested and evaluated for the presence of micronuclei in polychromatic erythrocytes (PCE). One thousand polychromatic erythrocytes were evaluated per animal. Treatment-related signs included lethargy, hyperactivity, and aggressiveness. Treatment with the test material did not result in an increase in the number of micronuclei per 1000 PCE's. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 6/17/05)

DNA DAMAGE

** 0033; 215817; "Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes"; (R.H.C. San, J.E. Sly; Microbiological Associates, Inc., Rockville, MD; Study No. G95CB09.380); Primary rat hepatocyte cultures were exposed to SAN 1289 H Technical (lot no. 6663-50-1; purity: 96.3% (S-dimethenamid: 91.1%)) at concentrations ranging from 7.8 to 1000 μg/ml for 18 to 20 hours at 37° C. Vehicle and positive (DMBA, 10 μl/ml) controls were included in the assay. There were 3 cultures/treatment level. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 6/17/05)

NEUROTOXICITY

Study not submitted nor required at this time.

METABOLISM STUDIES

** 0042; 215840; "SAN 582 H: Absorption, Distribution, Metabolism, and Excretion of [^{14}C] SAN 582H in Rats after Single and Multiple Doses"; (S. Vollmin, A. Schweitzer; Sandoz Agro Ltd., Development Region Basle, Analytical Chemistry and Environmental Sciences, CH-4002 Basle, Switzerland; Study No. 87.03.01; 2/6/92); Three sets of studies were performed in which Kfm:WIST rats of both sexes were treated with [^{14}C] SAN 582H (batch no. RA 683-1, specific radioactivity: 157 uCi/mg; radiochemical purity: 99.9%). The specific activity of the dosage preparations was adjusted by supplements of unlabeled SAN 582H (batch no. 6083, purity: 99.8%). In the Excretion study, 6 animals/sex/group were dosed orally by gavage with 10 or 1000 mg/kg, by intravenously with 10 mg/kg of the radiolabeled test material or with 10 mg/kg/day for 14 days with unlabeled test material, followed by a single 10 mg/kg dose of radiolabeled test material. Urine and feces were collected at specified intervals up to 7 days post-dose. In addition, two groups of three animals/sex were dosed orally with 10 mg/kg of the radiolabeled test material. From one group of bile-cannulated rats, bile as well as urine and feces was collected at specified intervals up to 7 days post-dose. Carbon dioxide as well as urine and feces was collected up to 48 hours post-dose from the other group of animals. In the Blood Kinetics Study, 3 rats/sex/group were dosed orally with 10 or 1000 mg/kg or intravenously with 10 mg/kg with the radiolabeled test material. Blood was collected periodically up to 7 days post-dose. In the Tissue Distribution Study, 12 animals/sex/group were dosed orally with 10 or 1000 mg/kg of the radiolabeled test material and 3 animals/sex/group/time point were euthanized at 1, 4, 24 or 72 hours post-dose and selected tissues were analyzed for the presence of radiolabel. In addition, the tissues of 3 animals/sex/group from the 4 different treatments in the Excretion Study euthanized 7 days post-dose were analyzed. In the Excretion Study, two of the 5 males in the 1000 mg/kg group died. In the Blood Pharmacokinetic Study, one of the 3 males in both the 10 and 1000 mg/kg groups died. In the Tissue Distribution Study, two of 3 males and two of 2 females of the 1000 mg/kg group scheduled for tissue sampling at 72 hours post-dose died. For the animals treated with 10 mg/kg orally, 96 to 97% of the administered dose was absorbed (see study in which the bile duct was cannulated). Seventy five to 82% of the dose was recovered in the bile. Eighty to 82% of the administered dose was recovered via excretion within the first 24 hours post-dose. Excretion of the radiolabel in carbon dioxide was quite minimal. Excretion of the radiolabel in the urine was higher for the females than for the males when the animals were dosed at 10 mg/kg ((M) 31 to 35% vs. (F) 47 to 53%). Excretion in the feces was similarly greater for the males ((M) 56 to 62% vs. (F) 37 to 48%). The route or frequency of treatment did not particularly affect this ratio. When the animals were treated with 1000 mg/kg, there was no apparent sexual difference in the excretion profile (urine: 62 to 63%, feces: 26 to 30%). For the animals treated with 10 mg/kg, 55 to 70% of the administered dose was recovered within the first 24 hours. In contrast, only 17 to 19% of the administered dose was recovered within the first 24 hours post-dose from the animals treated with 1000 mg/kg. In the Blood Kinetic Study, for the animals which were dosed orally, the peak blood levels were achieved only after 24 to 48 hours post-dose and were still quite elevated at 7 days post-dose. In the animals treated intravenously, peak levels were achieved more rapidly and were sustained through out the 7 day period. In the Tissue Distribution Study, the radiolabel was predominantly recovered in the whole blood and the spleen over the course of the 7 day collection period. There was only a negligible amount of label in the plasma. Initially, the liver and kidneys were primary sites of radiolabel recovery. The recovery from these tissues declined over the 7 day study period. The radiolabel was predominantly recovered in the whole blood and spleen at 7 days post-dose no matter whether the route of dosing was oral or intravenous or the dose level was 10 mg/kg or 1000 mg/kg. The primary pathway of metabolism for the test material was through glutathione conjugation. The resulting metabolites were products of the breakdown of the glutathione conjugate via 1) the

mercapturic acid pathway, 2) to a cysteine conjugate followed by oxidation to the thiolactic acid conjugate and then by further oxidation to the sulfoxide of this conjugate or 3) to the mercaptan which was further modified by S-methylation and succeeding alterations. Additional pathways included the direct modification of the parent compound by demethylation and the oxidation of the methyl groups on the thiophene ring. Dechlorination of the compound and oxidation of the sulfur in the thiophene ring also occurred. Glucuronide and/or sulfate conjugates of metabolites were recovered from the urine, feces and bile. **Study acceptable.** (Moore, 7/18/05

0043; 215842; "SAN 582 H: Determination of the Presence of Plant Metabolites in Rat"; (C.C. Yu, A.S. Guirguis, D.A. Nietschmann; Metabolism & Pharmacokinetics Section, Sandoz Agro Inc., Des Plaines, IL; Report No. 28A; 11/18/92); Five CD rats/sex/group were dosed orally by gavage with 1 or 100 mg/kg of [^{14}C] SAN 582H (lot no. RA 683-2 Ch 901101, radiochemical purity: 98%, specific activity: 50.56 mCi/mmole). The purity of the unlabeled test material was not reported. Urine and feces were collected daily for 3 days. The urine and feces from the individual animals in the respective groups were pooled over the 3 day period in order to analyze for the presence of the plant metabolites, SAN 582H sulfonate, SAN 582 H sulfoxide of thioglycolic acid, and SAN 582H thioglycolic acid, in the excretory products. Isolation and purification of these metabolites by thin layer chromatography revealed that SAN 582 H sulfonate comprised 0.025 and 0.03% of the urine radiolabel and 0.016 and 0.02% of the fecal radiolabel in the 1 and 100 mg/kg group animals, respectively. The sulfoxide of thioglycolic acid derivative comprised 0.007 and 002% of the radiolabel recovered in the urine of the 1 and 100 mg/kg group animals, respectively. The SAN 582H thioglycolic acid derivative was not recovered in any of the samples. **Study supplemental.** (Moore, 7/19/05)

52984-0045; 215846; "SAN 582H: Addendum to Determine Sulfoxide of Thioglycolic Acid Conjugate in Mouse Excreta"; (M.L. Ekdawi, C.C. Yu; Metabolism & Pharmacokinetics Section, Sandoz Agro, Inc., Des Plaines, IL; Report No. 26; 9/22/92); Five CD-1 mice/sex/group were dosed orally by gavage with 1 or 100 mg/kg of [^{14}C] SAN 582H (lot no. RA 683-2 Ch 901101, radiochemical purity: 98.6%, specific activity: 50.5 mCi/mmole). The purity of the unlabeled test material was not reported. Urine and feces were collected daily for 4 days. The urine and feces from the individual animals in the respective groups were pooled over the 4 day period in order to analyze for the presence of the plant metabolite, sulfoxide of the SAN 582H thioglycolic acid conjugate in the excretory products. Isolation and purification of the metabolite by thin layer chromatography revealed that the sulfoxide comprised 0.25 and 0.24% of the urine radiolabel and 0.25 and 0.4% of the fecal radiolabel in the 1 and 100 mg/kg group animals, respectively. **Study supplemental.** (Moore, 7/19/05)

52984-0045; 215845; "SAN 582H: Determination of the Presence of Sulfonate Metabolite in Mice"; (M.L. Ekdawi, C.C. Yu; Metabolism & Pharmacokinetics Section, Sandoz Agro, Inc., Des Plaines, IL; Report No. 25; 6/11/92); Five CD-1 mice/sex/group were dosed orally by gavage with 1 or 100 mg/kg of [^{14}C] SAN 582H (lot no. RA 683-2 Ch 901101, radiochemical purity: 98.6%, specific activity: 50.5 mCi/mmole). The purity of the unlabeled test material was not reported. Urine and feces were collected daily for 4 days. The urine and feces from the individual animals in the respective groups were pooled over the 4 day period in order to analyze for the presence of the plant metabolite, SAN 582H sulfonate in the excretory products. Isolation and purification of the metabolite by thin layer chromatography revealed that SAN 582 H sulfonate comprised 0.06 and 0.069% of the urine radiolabel and 0.25 and 0.25% of the fecal radiolabel in the 1 and 100 mg/kg group animals, respectively. **Study supplemental.** (Moore, 7/19/05)

SUBCHRONIC STUDIES

Rat 5-Week Dietary Toxicity Study

52984-0175; 219004; "SAN 582 H: 5-Weeks Pilot Feeding Study in Rats"; (S. Carpy, S.F.P. Warren, F. Muller, J. Karapally; Sandoz Ltd., Agro Development, Toxicological Department, Basle, Switzerland; Study ID No. 363-R; 10/27/86); Eight Han-Wistar rats/sex/group received 0,

30, 100, 300, 1000, or 3000 ppm of SAN 582 H (lot no. March 27, 84, purity: 99%) in the diet for 5 weeks ((M) 0, 2.92, 9.5, 28.8, 95.6, 285 mg/kg/day; (F) 0, 3.32, 10.8, 35.7, 109, 328 mg/kg/day). The mean body weight of the 3000 ppm males was less than that of the control from the 1st week on ($p<0.05$ or 0.01). The mean food consumption of the 3000 ppm males was less than that of the control for the 1st week of the study ($p<0.01$). There were no treatment-related effects noted in the hematology and urinalysis. In the serum chemistry, the mean cholesterol concentration was increased for both sexes in the 3000 ppm group ((M) $p<0.05$), (F) NS). The mean absolute and relative liver weights of the 3000 ppm females and the mean relative liver weights of the 3000 ppm males were greater than those values for the control animals ($p<0.01$). In the histopathology examination, the incidence of centrilobular cytoplasmic swelling was noted in the liver of both sexes of the 3000 ppm group (M/F) 0: 0/8 vs. 3000: 4/8). **No adverse effect indicated. 5-week dietary toxicity NOEL:** (M/F) 1000 ppm ((M) 95.6 mg/kg/day, (F) 109 mg/kg/day) (based upon treatment-related effects upon the liver of the 3000 ppm group); **Study supplemental** (non-guideline study). (Moore, 8/26/05)

Rat Subchronic Dietary Toxicity Study

52984-0031; 215808; "A Subchronic (3-Month) Toxicity Study of SAN 1289 H in the Rat Via Dietary Administration"; (D.L. Blanset; Huntingdon Life Sciences, East Millstone, NJ; Study No. 95-2401; 11/15/96); Ten Sprague-derived rats/sex/group received 0, 500, 1500 or 3000 ppm of SAN 1289 H; batch no. 6663-50-1, purity:96.3% (dimethenamid), 91.1% (S-dimethenamid) in the diet for 13 weeks ((M) 0, 37, 110, 222 mg/kg/day, (F) 0, 40, 125, 256 mg/kg/day). No deaths resulted from the treatment. The mean body weight gain for the males in the 3000 ppm group was lower than that of the controls during the first 4 weeks of the study ($p<0.05$). There was no treatment related effect upon the mean food consumption. The treatment did not result in an apparent effect upon the urinalysis or hematology parameters. In the clinical chemistry evaluation, the serum gamma-glutamyl transpeptidase (GGT) activity and cholesterol level were elevated for the males in the 3000 ppm group ($p<0.01$). The GGT activity was also increased for the 1500 ppm males ($p<0.05$). The mean absolute and relative liver weights for both sexes in the 3000 ppm group and the mean relative liver weights for the 500 ppm males and for both sexes in the 1500 ppm group were greater than those values of the controls ($p<0.01$). In the histopathological examination, the females in the 500 ppm group and above demonstrated centrilobular hypertrophy of the hepatocytes (0: 0/10 vs. 500: 3/10, 1500: 8/10, 3000: 8/10). The females in the 1500 and 3000 ppm groups also suffered hepatic necrosis (0: 0/10 vs. 1500: 5/10, 3000: 4/10). The males in the 1500 and 3000 ppm groups exhibited periportal hypertrophy of the hepatocytes (0: 0/10 vs. 1500: 8/10, 3000: 10/10). There were also eosinophilic inclusions in the periportal region of the liver of the 1500 and 3000 ppm males (0: 0/10 vs. 1500: 3/10, 3000: 7/10). **Possible adverse effect:** hepatic necrosis. **Subchronic NOEL:** (M) 500 ppm (37 mg/kg/day) (based upon treatment-related effects upon the liver noted for the males in the 1500 ppm group); (F) <500 ppm (40 mg/kg/day) (based upon the incidence of centrilobular hypertrophy noted for the females in the 500 ppm group); **Study acceptable.** (Moore, 6/8/05)

52984-0174; 219003; "SAN 582 H: Toxicity Study in Rats by Repeated Dietary Administration for 13 Weeks followed by a 4-Week Withdrawal Period"; (S.A. Ruckman, *et. al.*; Department of Rodent Toxicology, Huntingdon Research Centre, Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. SDZ 327/87318; 10/16/86); Ten Sprague-Dawley rats/sex/group received 0, 50, 150, 500, 1500 or 3000 ppm of SAN 582 H (batch no. 8605; purity: 91.5%) in the diet for 13 weeks ((M) 0, 3.5, 10.0, 33.5, 98, 204 mg/kg/day, (F) 0, 3.9, 11.8, 40.1, 119, 238 mg/kg/day). An additional 10 animals/sex/group were included in the 0 and 3000 ppm groups and were maintained for 4 additional weeks after termination of the treatment. No deaths occurred during the study. The mean body weight gain of both sexes in the 1500 and 3000 ppm groups was less that that of the control over the 13 week treatment period ($p<0.05$ or 0.01). Mean food consumption was slightly lower for both sexes in the 3000 ppm treatment group in comparison to the control. No treatment-related effects were evident in the hematology, urinalysis or ophthalmology evaluations. In the clinical chemistry evaluation, the mean total serum protein was increased for both sexes in the 1500 and 3000 ppm groups ($p<0.01$). The mean albumin levels

were increased for the males in the 150 ppm group and above (p<01). The mean globulin levels for the females in the150 ppm group and above were greater than that of the control (p<0.05 or 0.01). The mean blood urea nitrogen levels were elevated for the 1500 and 3000 ppm males (p<0.05 or 0.01). The mean serum gamma-glutamyl transpeptidase activities were elevated for both sexes in the 3000 ppm group (p<0.01). The mean serum cholesterol concentrations were increased for the 1500 ppm females and for both sexes in the 3000 ppm group (p<0.01). In the necropsy examination, the mean adjusted liver weights for the 1500 ppm females and for both sexes in the 3000 ppm group were greater than those of the controls (p<0.01). In the microscopic examination of the liver, the incidence of enlarged centrilobular hepatocytes was noted for the 500 ppm females and above (0: 0/10 vs. 500: 1/10, 1500: 9/10, 3000: 10/10). **No adverse effect indicated. Subchronic Dietary NOEL (M/F):** 150 ppm ((M) 10.0 mg/kg/day, (F) 11.8 mg/kg/day) (based upon increased cholesterol levels and presence of centrilobular hypertrophy in the liver of one of the females in the 500 ppm group); **Study acceptable.** (Moore, 8/30/05)

Rabbit Three-Week Repeated Dosing Study

52984-0035; 215820; "SAN 582H: 3-Week Dermal Study in Rabbits"; (J.P. Hopley, F. Muller, H.J. Chevalier; Sandoz Agro Division, Department of Toxicology, Basel, Switzerland; Project No. 416-RB; 12/11/89); The skin of five New Zealand White rabbits/sex/group was exposed to 0 (demineralized water), 50, 150 or 500 mg/kg/day of SAN 582 H technical (lot no. 8605, purity: 91.4%) for 6 hours per day, 5 days per week for 3 weeks under a semi-occlusive wrap. No deaths resulted from the treatment. There was no apparent treatment-related effect upon the mean body weight gain or food consumption. Dermal irritation was evident at the site of application in a dose-related manner. Six animals in the 50 mg/kg group demonstrated barely perceptible effects by the end of the study. In the 150 mg/kg group, all of the animals exhibited barely perceptible erythema and/or edema by the end of the treatment period. For the 500 mg/kg group, a well defined erythema and/or edema was noted for 6 of the animals by the end of the treatment with the other 4 exhibiting barely perceptible effects. There were no apparent treatment-related effects noted in the hematology evaluation. In the clinical chemistry evaluation, the serum phosphate levels were lower for both sexes in the 150 and 500 mg/kg groups (p<0.05 or 0.01). However, a dose-response was not indicated by the data. In the necropsy examination, measurement of the absolute or relative organ weights did not reveal any treatment-related effect. In the histopathological examination, the treated skin was affected in a dose-related manner with round cell infiltration, acanthosis and/or hyperkeratosis being noted at all of the treatment levels. **No adverse effect evident. Systemic Dermal Toxicity NOEL:** (M/F) 500 mg/kg/day (based upon the lack of an apparent treatment-related effect upon the highest treatment group); **Dermal Irritation NOEL:** (M/F) < 50 mg/kg/day (based upon the treatment-related dermal irritation noted for the 50 mg/kg/day treatment group); **Study acceptable.** (Moore, 6/28/05)

Dog Subchonic Dietary Toxicity Study

52984-0034; 215819; "SAN 582H: 13-Week Oral Toxicity Study in Dogs"; (R.J. Greenough, R. Goburdhun; Inveresk Research International, Musselburgh EH21 7UB, Scotland; Project ID. IRI 635563; 9/9/87); Four beagle dogs/sex/group received 0, 100, 750 or 2000 ppm of SAN 582H Technical (racemic mixture) (batch no. 8605; purity: 91.4%) in the diet for 13 weeks (uptake of the active ingredient in mg/kgday was not calculated). The mean body weight gain of the both sexes in the 2000 ppm group and the females in the 750 ppm group was less than that of the controls (p<0.01). The mean food consumption of the both sexes in the 2000 ppm group was less than that of the controls (p<0.05). The hematology and urinalysis examinations did not reveal any treatment-related effects. The mean serum alkaline phosphatase activities of both sexes in the 2000 ppm group were elevated above the activities of the controls during weeks 6 and 12 (p<0.01 or NS). The mean serum cholesterol levels for the females in the 2000 ppm group were elevated at 6 and 12 weeks (p<0.01, 0.001). The mean absolute and relative liver weights for both sexes in the 2000 ppm group were greater than those of the controls (p<0.01). The mean relative liver weight for the 750 ppm females was greater than that of the controls (p<0.05). In the histopathological examination, periportal hepatocellular vacuolation was noted in the livers of both sexes in the 750 and 2000 ppm treatment groups ((M/F) 0: 0/4 vs. 750: 1/4, 2000: 4/4). Sinusoidal dilatation was also evident in the livers of some of these animals ((M): 0: 0/4 vs. 2000:

3/4; (F) 0: 0/4 vs. 750: 1/4, 2000: 3/4). Target organ: liver; **No adverse effect indicated. Subchronic Dietary NOEL:** (M/F) 100 ppm (based upon the reduced body weight gain and treatment-related effects on the liver of both sexes in the 750 ppm group); **Study unacceptable**, possibly upgradeable with the calculation of a.i. uptake in mg/kg/day. (Moore, 6/21/05)

STUDIES ON METABOLITES

Rat Acute Oral Toxicity Studies

52984-0044; 215843; "Dimethenamid Oxalamide: Acute Oral Toxicity Study in the Rat"; (H.A. Cummins;Pharmaco LSR Ltd., Eye, Suffolk, IP23 7PX, England; Report No. 95/SAS066/0264; 3/17/95); Five CD rats/sex/group were dosed orally by gavage with 2000 or 5000 mg/kg of Dimethenamid Oxalamide (batch no. RS-582OXA-080194; purity: 99.83%) (vehicle: aqueous 0.5% (w/v) methylcellulose). No deaths resulted from the treatment. The animals in the high dose group demonstrated underactivity, pallor, piloerection, salivation, and hunched posture. The clinical signs were no longer evident within 2 days of dosing. No treatment-related lesions were evident in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; **Study acceptable.** (Moore, 7/19/05)

52984-0045; 215844; "Acute Oral Toxicity Study in Rats"; (D.L. Balsczak; Bio/dynamics, Inc., East Millstone, NJ; Study No. 92-6291; 9/14/92); Five CD rats/sex were dosed orally by gavage with 5000 mg/kg of SAN 582H Sulfonate Metabolite (lot no. 4997, purity: 99.45%) (vehicle: distilled water). No deaths resulted from the treatment. Clinical signs included yellow genital staining and watery or unformed stools. No treatment-related lesions were noted in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; **Study acceptable.** (Moore, 7/19/05)